Prostate-Specific Antigen and Long-Term Prediction of Prostate Cancer Incidence and Mortality in the General Population

David D. Ørsted, Børge G. Nordestgaard, Gorm B. Jensen, Peter Schnohr, Stig E. Bojesen

1. Introduction

Prostate cancer (PCa) is among the most common cancers worldwide [1] and is a leading cause of cancer death in men in the developed world [2]. Prostate-specific antigen (PSA) is a serine protease produced by prostatic epithelial cells [3], and in the event of prostatic disease, PSA leakage into the bloodstream increases. This characteristic makes...
measurement of plasma PSA an important element in the diagnosis of PCa; the measurement is used as a biomarker to determine the need for further examination.

Most previous studies on PSA and PCa were limited by short periods of follow-up, often used a case-control study design, and they had only 300–800 participants [4–6]; the studies examining PCa mortality were retrospective or case-control studies only [7–9]. Two population-based studies of 1800 and 5000 men aged 33–50 yr with 20–30 yr of follow-up showed that measurement of PSA could predict PCa incidence and stage at diagnosis; however, these studies did not examine PCa mortality and did not include men >50 yr [10,11]. Thus, it is largely unknown if PSA predicts long-term PCa incidence and stage at diagnosis; however, these studies did not examine PCa mortality and did not include men >50 yr [10,11].

We tested the hypothesis that PSA at first date of testing predicts long-term risk of PCa incidence and mortality. For this purpose, we measured PSA in samples collected in 1981–1983 from 4383 men from the general population (the Copenhagen City Heart Study) aged 20–94 yr and subsequently followed for 28 yr. For use in clinical practice, we also calculated 10-yr absolute risk estimates for PCa incidence and mortality as a function of baseline PSA levels.

2. Methods

2.1. Setting and participants

Study participants were men examined in 1981–1983 in the Copenhagen City Heart Study [12–15], thus, prior to the introduction of PSA testing into clinical practice in Denmark in 1995 [16]. Participants were selected randomly from the Danish Central Person Register to represent the general population.

Individual participants were followed in the Danish health registries from study entry in 1981–1983 and were censored at the occurrence of the end point in question (PCa, metastatic PCa, PCa death, or other deaths), emigration, or 31 December 2008, whichever came first. To test for the possible influence of PSA testing, we performed sensitivity analyses with end of follow-up on 31 December 1994.

Participants filled out a self-administered questionnaire that was reviewed by the participant and an investigator on the day of attendance. Participants reported on smoking habits and alcohol intake. Body mass index was measured (weight in kilograms divided by measured height in meters squared).

Information on diagnosis and stage of PCa (World Health Organisation [WHO] International Classification of Diseases, 7th edition code 177, and 10th edition code C61.9) was obtained from the Danish Cancer Registry, which identifies 98% of all incident cancers in Denmark [17]. All diagnoses in the registry are assigned based on histologic examination by a fully trained pathologist. Stage at diagnosis (1981–2004) was either localised, regional, metastatic, or unknown. Records on PCa mortality were drawn from the Danish Causes of Death Registry, which records information on death date and causes of death for all deaths in Denmark reported by hospitals and general practitioners [18].

The study was approved by Herlev Hospital and a Danish ethical committee (KF-100.2039/91). All participants gave written informed consent.

2.2. Biochemical analysis

Blood samples were drawn on the day of attendance, and after centrifugation plasma was stored at −20 °C. In 2010, samples were thawed, and after centrifugation, total PSA was measured immunochromically using the ADVIA Centaur XP Immunoassay (Siemens), which is traceable to the WHO (90:10) 96/670 PSA standard and has a range of measurement from 0.01 to 100 ng/ml. Samples with a PSA value >100 ng/ml were diluted and remeasured. Coefficient of variation was 6%, 3%, and 5% at PSA levels of 0.4, 2.0, and 11.0 ng/ml, respectively. Accuracy of the assay was regularly assessed by a Scandinavian external quality control programme. All analyses were performed using the same autoanalyzer operated by the same laboratory technician blinded to disease status.

2.3. Statistical analysis

Statistical analyses were performed using Stata 11.1 SE software. Two-sided p < 0.05 was significant. A priori we stratified baseline total PSA into six clinical categories (0.01–1.00, 1.01–2.00, 2.01–3.00, 3.01–4.00, 4.01–10.00, and >10.00 ng/ml); for trend tests these categories were assigned the values of 0, 1, 2, 3, 4, and 5. We chose the upper cut-off point of 10.00 ng/ml because previous studies have shown a high positive predictive value for PSA >10.00 ng/ml. We also examined PSA on a continuous scale using logarithmically transformed values.

We used Kaplan-Meier curves to plot cumulative incidences as a function of left-truncated age (with delayed entry) or as a function of time since blood sampling, as well as log-rank tests to examine differences between groups; death and emigration during follow-up led to censoring. We used the competing risk proportional subhazard regression model (Fine-Gray), which accounts for competing risk of death [19], to calculate subhazard ratios with 95% confidence intervals (CIs) for PCa incidence, metastatic PCa incidence, PCa mortality, and other deaths as a function of baseline PSA levels. Information on death (or emigration) is 100% accurate in Danish registries. Proportionality of hazards over time for PSA levels was assessed in a Cox proportional hazard regression model by plotting −log[−log(survival)] versus log(time), for nonparallel lines was further tested using Schoenfeld residuals. No major violations of the proportional hazard assumption were detected. Multivariate models were adjusted for age, smoking status, body mass index, and alcohol intake. We had 99.8% complete data on smoking status, body mass index, and alcohol intake. Missing values were imputed before multivariable adjustment for smoking with a code for missing values and for body mass index and alcohol intake based on age.

Absolute 10-yr risks of PCa incidence and mortality by levels of baseline PSA and age at blood sampling of <45, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and >75 yr were estimated using the regression coefficients from a Poisson regression model [20].

We calculated relative risk to enable readers to assess an individual patient's risk of PCa incidence and mortality compared with other patients of the same age, and we calculated absolute risk to provide estimates of individual risk for a foreseeable future of 10 yr; 10-yr absolute risk is used in prediction tools in other major diseases, for example, cardiovascular disease and breast cancer.

3. Results

We studied 4383 men from the Copenhagen City Heart Study. Follow-up was 100% complete. At time of blood sampling in 1981–1983, the median age of the cohort was 58 yr (interquartile range: 49–69 yr) (Table 1). Median age at blood sampling for men with a subsequent diagnosis of PCa was 63 yr, and for men who later died from PCa, median age at blood sampling was 62 yr (Fig. 1). Baseline characteristics for the entire study population and for participants according to PSA levels are shown in Table 1. Plasma PSA increased with age (p < 0.0001) (Table 1).
During 28 yr of follow-up, there were 170 cases of PCa, of which 56 cases were metastatic PCa at the time of diagnosis. There were 94 cases of PCa deaths. A total of 2914 participants died from other causes, and 21 participants emigrated. Median follow-up was 18 yr (range: 0.5–28 yr).

3.1. Cumulative incidence

The cumulative incidence of PCa and PCa death as a function of age increased stepwise for each PSA category (log rank, trend: \( p = 2 \times 10^{-66} \) and \( p = 9 \times 10^{-19} \)) (Fig. 2, left panels).

3.2. Relative risk

For PCa incidence, metastatic PCa incidence, and PCa mortality, subhazard ratios increased with increasing PSA levels at first date of testing (trend tests: \( p = 1 \times 10^{-60} \), \( p = 8 \times 10^{-20} \), and \( p = 2 \times 10^{-19} \)), while this was not the case for other deaths (trend test: \( p = 0.22 \)) (Fig. 3). For PCa during the entire follow-up period, the subhazard ratio was 3.0 (95% CI, 1.9–4.6) for a PSA level of 1.01–2.00 ng/ml, 6.8 (95% CI, 4.2–11) for PSA 2.01–3.00 ng/ml, 6.6 (95% CI, 3.4–13) for PSA 3.01–4.00 ng/ml, 16 (95% CI, 10–25) for PSA

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**Table 1 – Baseline characteristics of men from the Danish general population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories by plasma prostate-specific antigen levels, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Percentile 0–74%</td>
<td>58</td>
</tr>
<tr>
<td>Percentile 75–89%</td>
<td>50</td>
</tr>
<tr>
<td>Percentile 90–94%</td>
<td>45</td>
</tr>
<tr>
<td>Percentile 95–96.5%</td>
<td>45</td>
</tr>
<tr>
<td>Percentile 96.6–99.3%</td>
<td>45</td>
</tr>
<tr>
<td>Percentile 99.4–100%</td>
<td>45</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>64</td>
</tr>
<tr>
<td>Body mass index, kg/m² (range)</td>
<td>25.6 (23.5–28.0)</td>
</tr>
<tr>
<td>Alcohol, g/wk (range)</td>
<td>108 (36–228)</td>
</tr>
</tbody>
</table>

Values are expressed as number, fraction, or median (interquartile range).

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**Fig. 1 – Distribution of age at blood sampling for participants, regardless of prostate-specific antigen (PSA) values. Density designates the relative frequency of the different ages, and the area under each curve is 100%. Curves are shown for men who did not develop prostate cancer (PCa) and (a) for men who later developed PCa or (b) for men who died from PCa. Based on 4383 men from the Copenhagen City Heart Study, with PSA measured in samples from 1981 to 1983. Distributions were smoothed using a Gaussian kernel.**
4.01–10.00 ng/ml, and 57 (95% CI, 32–104) for PSA >10.00 ng/ml versus 0.01–1.00 ng/ml. For PCa mortality, corresponding subhazard ratios were 2.2 (95% CI, 1.3–3.9), 5.1 (95% CI, 2.8–9.0), 4.2 (95% CI, 1.8–10), 7.0 (95% CI, 3.8–14), and 14 (95% CI, 6.0–32). For follow-up from 1981 to 1994, the period before clinical PSA testing was generally available, results were similar (Fig. 3). If we further divided PSA levels >10 ng/ml, the subhazard ratios for PCa were 61 (95% CI, 30–123) for a PSA level of 10.01–20.00 ng/ml and 54 (95% CI, 22–132) for a PSA >20 ng/ml versus 0.01–1.00 ng/ml.

**Fig. 2 – Cumulative incidence of prostate cancer (PCa) and PCa death as a function of (left panels) left-truncated age with delayed entry and (right panels) time since blood sampling, stratified by prostate-specific antigen (PSA) levels. Based on 4383 men from the Copenhagen City Heart Study with PSA measured in samples from 1981 to 1983 and subsequently followed for 28 yr.**
Fig. 3 – Subhazard ratios for prostate cancer (PCa), metastatic PCa, PCa death, and other deaths by increasing levels of prostate-specific antigen (PSA). Based on 4383 men from the Copenhagen City Heart Study with PSA measured in samples from 1981 to 1983 and subsequently followed for 28 yr. The subhazard ratios were adjusted for age, smoking status, body mass index, and alcohol intake.

CI = confidence interval.
Corresponding subhazard ratios for PCa mortality were 13 (95% CI, 4–37) and 16 (95% CI, 5–51).

On a continuous scale, a doubling in PSA concentration resulted in a multivariate-adjusted subhazard ratio of 1.8 (95% CI, 1.7–2.0) for PCa and 1.6 (95% CI, 1.4–1.8) for PCa mortality (Table 2). After stratification for age, smoking status, body mass index, and alcohol intake, these subhazard ratios remained increased in all strata. For PCa and PCa death

<table>
<thead>
<tr>
<th>Stratification</th>
<th>Participants/Events, no.</th>
<th>Incidence rate/10 000 (95% CI)</th>
<th>PCa Subhazard ratio (95% CI)</th>
<th>Interaction</th>
<th>PCa death Subhazard ratio (95% CI)</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>170/4213</td>
<td>10 (9–12)</td>
<td>1.8 (1.7–2.0)</td>
<td>–</td>
<td>94/4289</td>
<td>5 (4–7)</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 (71%)</td>
<td>3107/106</td>
<td>8 (7–10)</td>
<td>1.9 (1.7–2.2) p = 0.09</td>
<td>3144/89</td>
<td>5 (4–7)</td>
<td>1.8 (1.5–2.1) p = 0.57</td>
</tr>
<tr>
<td>&gt;65 (29%)</td>
<td>1106/64</td>
<td>17 (13–21)</td>
<td>2.1 (1.9–2.3)</td>
<td>1145/25</td>
<td>6 (4–10)</td>
<td>2.0 (1.5–2.6)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (36%)</td>
<td>1509/70</td>
<td>11 (9–14)</td>
<td>2.0 (1.7–2.3) p = 0.24</td>
<td>1539/40</td>
<td>6 (5–9)</td>
<td>1.7 (1.5–2.1) p = 0.68</td>
</tr>
<tr>
<td>Yes (64%)</td>
<td>2704/100</td>
<td>9 (8–11)</td>
<td>1.7 (1.6–1.9)</td>
<td>2750/54</td>
<td>5 (4–7)</td>
<td>1.6 (1.3–1.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25 (41%)</td>
<td>1791/63</td>
<td>9 (7–11)</td>
<td>1.6 (1.5–1.8) p = 0.11</td>
<td>1821/33</td>
<td>5 (3–6)</td>
<td>1.3 (1.1–1.7) p = 0.21</td>
</tr>
<tr>
<td>&gt;25 (59%)</td>
<td>2422/107</td>
<td>11 (9–13)</td>
<td>2.1 (1.9–2.3)</td>
<td>2468/61</td>
<td>6 (5–8)</td>
<td>1.9 (1.6–2.2)</td>
</tr>
<tr>
<td>Alcohol, g/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤168 (64%)</td>
<td>2791/113</td>
<td>10 (8–12)</td>
<td>1.8 (1.7–2.0) p = 0.26</td>
<td>2839/65</td>
<td>6 (5–7)</td>
<td>1.7 (1.5–1.9) p = 0.60</td>
</tr>
<tr>
<td>&gt;168 (36%)</td>
<td>1422/57</td>
<td>10 (8–13)</td>
<td>1.9 (1.6–2.2)</td>
<td>1450/29</td>
<td>5 (3–7)</td>
<td>1.6 (1.2–2.1)</td>
</tr>
</tbody>
</table>

PCa = prostate cancer; CI = confidence interval.
Values presented are subhazard ratios with 95% CIs adjusted for all other covariates than the one stratified on. Testing for interaction of baseline prostate-specific antigen levels with age, smoking status, body mass index, and alcohol intake on risk of PCa and PCa death was done by introducing two-factor interaction terms in multifactorially adjusted Cox models.

![Fig. 4](image-url) - The absolute 10-yr risk of prostate cancer, in percentage, by baseline prostate-specific antigen (PSA) levels and age at blood sampling. Based on 4383 men from the Copenhagen City Heart Study with PSA measured in samples from 1981 to 1983 and subsequently followed for 28 yr.
there was no interaction between doubling of PSA and age, smoking status, body mass index, or alcohol intake (all \( p > 0.05 \)).

### 3.3. Absolute risk

For PCa, the absolute 10-yr risk increased stepwise with increasing PSA levels and with increasing age (Fig. 4). In men with a PSA level of 0.01–1.00 ng/ml, absolute 10-yr risk of PCa was 0.6% for age <45 yr, 0.7% for 45–49 yr, 1.1% for 50–54 yr, 1.2% for 55–59 yr, 1.3% for 60–64 yr, 1.1% for 65–69 yr, 1.3% for 70–74 yr, and 1.5% for ≥75 yr; corresponding values for PSA levels >10.00 ng/ml were 35%, 41%, 63%, 71%, 77%, 69%, 75%, and 88%, respectively.

For PCa mortality, absolute 10-yr risk increased stepwise with increasing PSA levels and age ≤65 yr (Fig. 5). In men with a PSA level of 0.01–1.00 ng/ml, the absolute 10-yr risk of PCa mortality was 0.3% for age <45 yr, 0.4% for 45–49 yr, 0.5% for 50–54 yr, 0.9% for 55–59 yr, 1.4% for 60–64 yr, 0.7% for 65–69 yr, 0.6% for 70–74 yr, and 0.5% for ≥75 yr; corresponding values for PSA levels >10.00 ng/ml were 9.8%, 16%, 20%, 35%, 52%, 28%, 22%, and 20%, respectively.

### 4. Discussion

The main finding of this study of 4383 men from the Danish general population was that stepwise increases in PSA at first date of testing predicted a 3- to 57-fold increased risk of PCa and a 2- to 16-fold increased risk of PCa mortality during 28 yr of follow-up. For use in clinical practice, we calculated an absolute 10-yr risk of PCa of 0.6–1.5% in men with PSA levels of 0.01–1.00 ng/ml and 35–88% in men with levels >10.00 ng/ml. These findings are novel, particularly for PCa mortality and specifically for men >50 yr.

A possible mechanism behind the present results may be that the development of PCa and leakage of PSA into the blood begin many years before the appearance of any symptoms, either because of premalignant changes or very low numbers of tumour cells. Our findings may theoretically also be due to effects of PSA that directly promote tumour growth and metastatic capabilities [3]. Finally, lifestyle and/or genetic factors influencing both PSA levels and the development of PCa might explain our findings [21]. Irrespective of which of these possible mechanisms operate, our findings clearly demonstrate that increasing levels of PSA predict long-term increases in risk of PCa incidence and mortality.
The present study is the first prospective general population study of risk of PCa mortality as a function of baseline PSA level. Previous studies on PCa mortality were either retrospective or case-control studies [7–9], and therefore inherent to biases not relevant for a prospective study of the general population. Our results of a strong association between increased PSA levels and increased risk of PCa mortality even at PSA levels below common thresholds for biopsy, 3.00 or 4.00 ng/ml [22,23], suggest that the development of surveillance programmes for men even at lower PSA levels may be justified. Furthermore, our results on PCa mortality support the idea that the findings on PCa incidence are clinically relevant and not driven by detection of insignificant PCa.

Our findings on PCa incidence and metastatic PCa are supported by results from previous studies examining the association between PSA levels and risk of PCa [4–6,10,11,24]. However, the results from previous studies have not been sufficiently convincing to influence screening recommendations, and the optimal strategy for PCa screening remains undetermined and widely debated in the medical community [25–29].

The potential clinical usefulness of our data should be considered. Our calculations of 10-yr absolute risk of PCa could be directly implemented as a clinical tool for advising individual patients and their physicians in a clinical setting stratified by age of the patient. For men with PSA levels ≤1.00 and 1.01–2.00 ng/ml, the absolute 10-yr risk of PCa was ≤1.5% and ≤4.5%, respectively, irrespective of age. Such information could be used to reassure men and possibly reduce their need for further PSA testing, particularly in individuals with PSA ≤1.00 ng/ml. Previous studies have suggested that the optimal screening intervals for this group might be 4–8 yr [30–32]. However, our results imply that these intervals may be prolonged, thereby further reducing the number of PSA tests currently performed. For men <50 yr with PSA 2.01–4.00 ng/ml, the absolute 10-yr risk of PCa was moderately elevated up to 5.6%. The 2-yr absolute risk of PCa for the same men was 0.6% (data not shown); whether these estimates constitute an acceptable risk or whether men with these levels should have further testing within a shorter time period should be decided by the individual patient and his physician. However, for men ≥50 yr with PSA 2.01–4.00 ng/ml, the absolute 10-yr risk of PCa ranged from 7.1% to 12%, risks that in many countries would lead to close monitoring of the patient with frequent PSA measurements, digital rectal examination, and transrectal ultrasonography. Finally, our data support the idea that in men with PSA levels of 4.01–10.00 ng/ml, and particularly with PSA >10.00 ng/ml, detailed examination for the presence of PCa would be warranted. The present data would be best used when viewed together with other existing data during revision of guidelines on how best to use PSA measurement and on how best to screen for PCa in an attempt to reduce morbidity and mortality without causing unnecessary anxiety. Also, showing Figures 4 and 5 to patients may help them understand that an elevated PSA level is not the same as a diagnosis of PCa or a finding that they will die from PCa, but that the level can be used to predict long-term risks. This idea, together with potential side-effects of the treatments offered for PCa, can be discussed between the physician and patient to make an informed joint decision of the best continued monitoring strategy, treatment, or both.

When we examined the absolute 10-yr risk of PCa death, we found increasing risk for men ≤65 yr, after which the risk of PCa death attenuated. This finding is likely caused by increased risk of death from competing events in men >65 yr, as previously shown [33]. Nonetheless, this finding suggests that our results for 10-yr risk of PCa death could be valid even though we did not have complete information on treatment and PCa stage at diagnosis.

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**Fig. 6 – Cumulative incidence of prostate cancer as a function of age, for responders and nonresponders to the Copenhagen City Heart Study 1981–1983 examination.** Based on 4383 men who responded to the Copenhagen City Heart Study and 2597 men who did not attend the Copenhagen City Heart Study. The subhazard ratio was adjusted for age. The competing event was death from causes other than PCa.
Our study has several strengths. The study population is representative of the male general population, follow-up was >28 yr and 100% complete, and the study population is well characterised. Also, PSA was not introduced into clinical practice in Denmark until 1995 [16,34], thus many years after blood sampling in this cohort, and PSA measurement is still not recommended for general population–screening purposes in Denmark. Thus, the PCa cases in the present study are unlikely to be chance findings due to widespread PSA screening but rather were diagnosed after patients presented with symptoms. This situation may explain the relatively high 10-yr risk of PCa death in age groups <65 yr at blood sampling compared with the 10-yr risk of PCa in the same group of men. Indeed, the results when follow-up ended at the end of 1994, at the time of introduction of PSA testing into general clinical practice in Denmark, were similar to the results for the entire follow-up. Additionally, because PSA concentrations were measured almost 30 yr after blood sampling and thus not reported to participants or their physicians, these measurements have not influenced ascertainment of PCa during follow-up. Another strength was that we were able to examine the risk of PCa mortality with increasing PSA levels (as opposed to examining PCa incidence only), which adds yet more credibility to the results. Finally, when we examined risk of other deaths, we found similar risk with increasing baseline PSA levels.

A limitation of our study is that our study population only included white participants of Danish descent, and thus our results may not necessarily apply to other ethnic groups. Another potential limitation is that we did not have information on family history of PCa, clinical PSA testing, previous prostate biopsies, or digital rectal examination. Yet another potential limitation is possible selection bias, such that healthy rather than diseased individuals attend such an examination; however, when we compared nonresponders (30%) and responders (70%), we found a similar incidence of PCa among nonresponders and responders (Fig. 6). Finally, a potential limitation is that for calculation of risk of PCa mortality, we did not have information on stage at diagnosis or treatment.

5. Conclusions

Stepwise increases in PSA level at first date of testing predicted a 3- to 57-fold increased risk of PCa, a 2- to 16-fold increased risk of PCa mortality, and a 35–88% absolute 10-yr risk of PCa in men with PSA levels >10.00 ng/ml. Equally important, the absolute 10-yr risk of PCa in men with PSA 0.01–1.00 ng/ml was only 0.6–1.5%. These results may be useful during revisions of guidelines on the use of PSA testing in healthy men.

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References


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Acquisition of data: Ørsted, Nordestgaard, Jensen, Schnohr, Bojesen.

Analysis and interpretation of data: Ørsted, Nordestgaard, Bojesen.

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